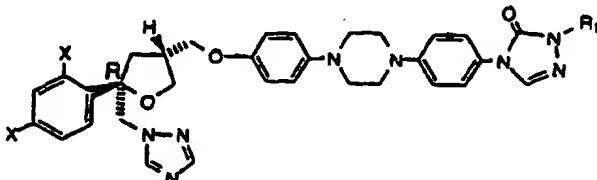




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : A61K 31/495, 47/48</p>	<p>A1</p>	<p>(11) International Publication Number: WO 99/27932</p> <p>(43) International Publication Date: 10 June 1999 (10.06.99)</p>
<p>(21) International Application Number: PCT/US98/24938</p> <p>(22) International Filing Date: 30 November 1998 (30.11.98)</p> <p>(30) Priority Data: 08/980,950 1 December 1997 (01.12.97) US</p> <p>(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).</p> <p>(72) Inventor: NARINGREKAR, Vijay, H.; 812 Pascack Road, Paramus, NJ 07652 (US).</p> <p>(74) Agents: HOFFMAN, Thomas, D. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).</p>		<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, GR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: INJECTABLE ANTIFUNGAL FORMULATIONS</p> <div style="text-align: center;">  <p>(I)</p> </div> <p>(57) Abstract</p> <p>A pharmaceutical composition suitable for parenteral administration comprising an antifungally effective amount of a compound represented by formula (I), wherein X is independently both F or both Cl or one X is independently F and the other is independently Cl; R₁ is a straight or branched chain (C₄-C₅) alkyl group substituted by a hydroxy moiety; and an effective amount of maltosyl-β-cyclodextrin, is disclosed.</p>		

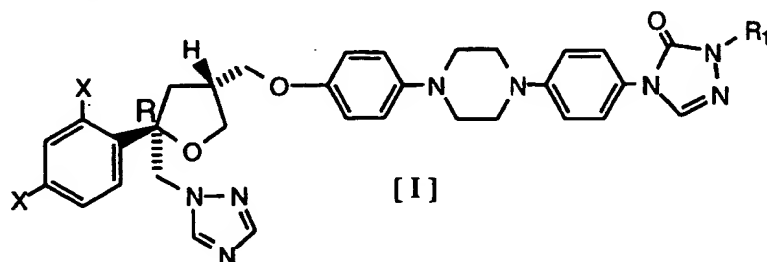
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Injectable Antifungal Formulations

This invention relates to pharmaceutical compositions suitable for parenteral administration comprising an antifungally effective amount of a compound represented by formula I



wherein X is independently both F or both Cl or one X is independently F and the other is independently Cl; R₁ is a straight or branched chain (C₄-C₅) alkyl group substituted by a hydroxy moiety; and an effective amount of maltosyl- β -cyclodextrin or glucosyl- β -cyclodextrin.

Compounds of formula I are disclosed in U.S. Patent 5,661,151 as exhibiting broad spectrum antifungal activity against the major fungal infections including candidosis, cryptococcosis, and aspergillosis as well as candidosis resistant to currently available antifungal agents such as fluconazole. Compounds represented by formula I exhibit broad spectrum antifungal activity in conventional antifungal screening tests, against human and animal pathogens, such as the following: *Aspergillus*, *Blastomyces*, *Candida*, *Cryptococcus*, *Coccidioides*, *Epidermophyton*, *Fonsecaea*, *Fusarium*, *Mucor*, *Saccharomyces*, *Torulopsis*, *Trichophyton*, *Trichosporon*, *Sporothrix* and *Pneumocystis*. The antifungal compounds of formula I are orally active but development of commercially viable injectable formulations for the compounds of formula I has been stalled due to the poor solubility of these compounds in aqueous and pharmaceutically acceptable non-aqueous solvents.

Over the past 30 years, fungal infections, especially the above listed major fungal infections, have become prevalent due to an increased number of immunocompromised patients (neutropenic cancer, bone marrow transplantation, solid organ transplant, HIV/AIDS), patients in intensive care units and patients with debilitating underlying diseases. The factors that place these patients at risk include: advanced life support interventions, cytotoxic chemotherapy or other types of immunosuppression surgical procedures, prolonged hospitalization and use of

broad-spectrum antibiotics. The major opportunistic fungal infections are candidiasis, aspergillosis and cryptococcosis. The incidence of nosocomial candidiasis and aspergillosis has dramatically increased in the last ten to fifteen years, and *Candida albicans* has emerged as a new pathogen causing life-threatening nosocomial infections. The market success of fluconazole in the 1990's has contributed to emergence of *Aspergillus sp.* and fluconazole-resistant *Candida sp.*

Morbidity and mortality from these major opportunistic fungal infections remain high despite the availability of antifungal agents. The less than optimal efficacy provided by current agents is further limited by: dose-limiting toxicity, development of fungal resistance, unreliable and unpredictable blood levels, and a limited spectrum of activity or limited dosage forms (i.e., orally only, IV only).

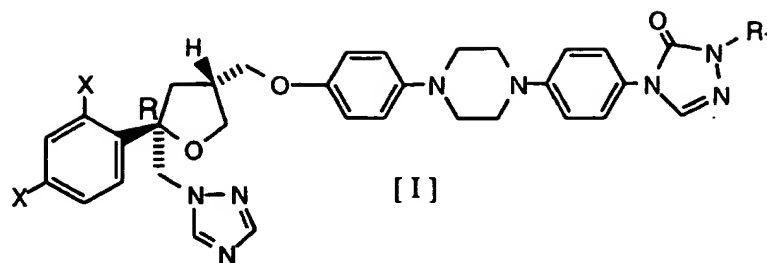
U.S. Patent No. 5,312,815 discloses inclusion complexes of the single antifungal agent, (+)-2-(2,4-difluorophenyl)-3-methyl-1-(1H-1,2,4-triazol-1-yl)-3-(6-(1H-1,2,4-triazol-1-yl)pyridazin-3-ylthio)butan-2-ol, and alpha-, beta- or gamma-cyclodextrins such as glucosyl- or maltosyl-cyclodextrin.

Thus, there is a need for an injectable dosage formulation of an antifungal agent that exhibits low toxicity and which is capable of maintaining improved efficacy against candidosis, cryptococcosis and aspergillosis.

Summary of the Invention

Surprisingly, we have discovered that aqueous solutions of glucosyl- β -cyclodextrin and maltosyl- β -cyclodextrin are able to solubilize the compounds of formula II to provide chemically stable pharmaceutical compositions suitable for parenteral administration, preferably intravenous administration.

Thus, the present invention provides a pharmaceutical composition comprising (a) an antifungally effective amount of a compound represented by the formula I

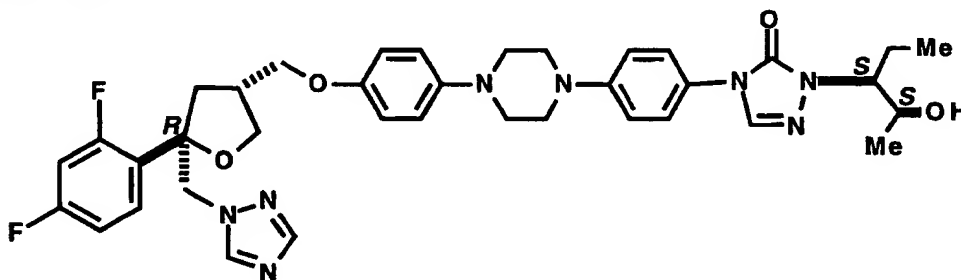


wherein X is independently both F or both Cl or one X is independently F and the other is independently Cl;

R₁ is a straight or branched chain (C₄-C₅) alkyl group substituted by a hydroxy moiety;
or a pharmaceutically acceptable salt thereof; and

- (b) an effective amount of one of maltosyl- β -cyclodextrin or glucosyl- β -cyclodextrin, and
- (c) a pharmaceutically acceptable carrier

The present invention also provides a pharmaceutical composition comprising (a) an antifungally effective amount of the compound represented by the formula II



or an ester of the OH group convertible *in vivo* into OH;
or a pharmaceutically acceptable salt thereof; and

- (b) an effective amount of one of maltosyl- β -cyclodextrin or glucosyl- β -cyclodextrin and

- (c) a pharmaceutically acceptable carrier

The pharmaceutical compositions of the present invention are chemically stable and are suitable for parenteral administration.

The present invention also provides a method of treating a susceptible fungal infection in mammals which comprises administering to a mammal afflicted with such a fungal infection an antifungally effective amount of the pharmaceutical compositions of the present invention.

Detailed Description of the Invention

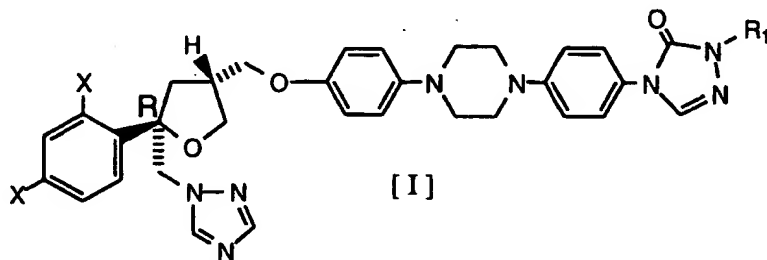
The term "glucosyl- β -cyclodextrin" as used herein means a β -cyclodextrin in which one of the free hydroxy moieties in each of the 7 glucose units in β -cyclodextrin has been substituted by glucosyl groups. See K. Koizumi, et al. Chem Pharm Bull. 35 (8)3413-3418 (1987). The preferred glucosyl- β -cyclodextrin is 6-O- α -D-glucosyl- β -cyclodextrin (G1- β -CD) which is available from Ensui Sugar Refining Co. Ltd., Yokohama, 230 Japan as mono G1- β -CD.

The term "maltosyl- β -cyclodextrin" as used herein means a β -cyclodextrin wherein one of the free hydroxy moieties in each of the seven (7) glucosyl units of β -cyclodextrin has been substituted by a maltosyl group by procedures such as disclosed in U.S. Patent 4,668,626 or the paper by Y. Okada et al. in Chem. Pharm. Bull. 36 (6) 2176-2185 (1998). The preferred maltosyl- β -cyclodextrin is 6-O- α -maltosyl- β -cyclodextrin ("G2- β -CD") available from Ensui Sugar Refining Co. Ltd. under the trade name mono-G2- β -CD.

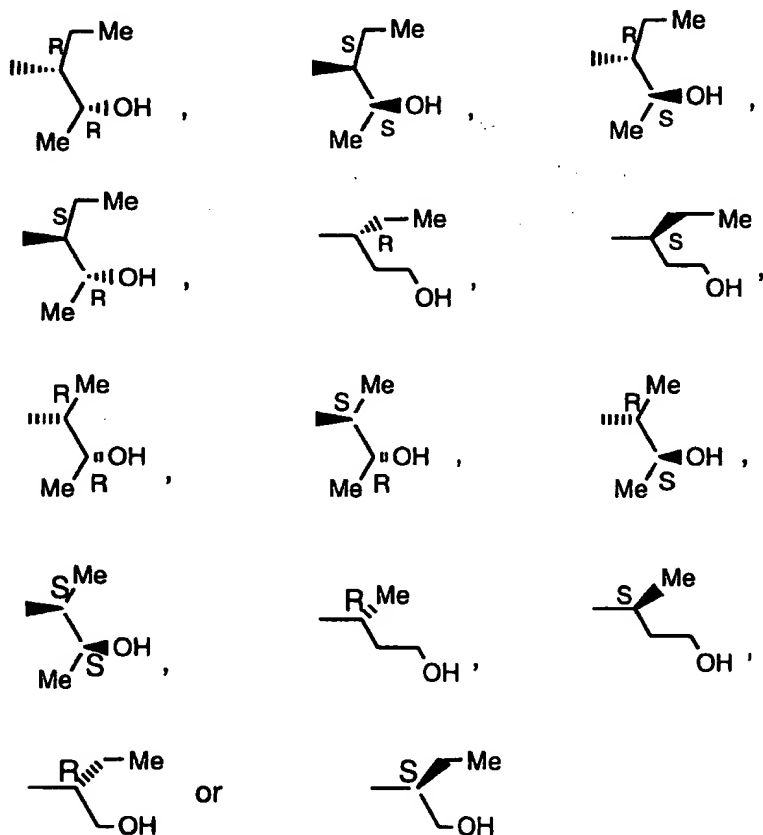
The term "susceptible fungal infections" includes the major opportunistic fungal infections such as candidiasis, aspergillosis and cryptococcosis. As noted herein above, the compounds represented by formula I, e.g., the compound of formula II, exhibit broad spectrum antifungal activity in conventional antifungal screening tests, against human and animal pathogens, such as the following: *Aspergillus*, *Blastomyces*, *Candida*, *Cryptococcus*, *Coccidioides*, *Epidemophyton*, *Fonsecaea*, *Fusarium*, *Mucor*, *Saccharomyces*, *Torulopsis*, *Trichophyton*,

Trichosporon, Sporothrix and Pneumocystis. The pharmaceutical compositions of the present invention are expected to exhibit similar antifungal activity.

In a preferred aspect of the present invention, the pharmaceutical compositions comprise an antifungally effective amount of a compound represented by formula I



wherein X is independently both F or both Cl or one X is independently F and the other is independently Cl; preferably each X is F, and R₁ is



The compounds of formulas I and II may be prepared in accordance with the procedures, schemes and examples of U.S. Patent No. 5,661,151.

The pharmaceutically acceptable salts of the compounds of the present invention include pharmaceutically acceptable acid and base addition salts.

The preferred pharmaceutically acceptable acid addition salts are nontoxic acid addition salts formed by adding to the compounds of the present invention about a calculated amount of a mineral acid, such as HCl, HBr, H₂SO₄, HNO₃ or H₃PO₄, or of an alkyl or arylsulfonic acid such as methanesulfonic, isithionic, paratoluenesulfonic, naphthylsulfonic and the like.

The pharmaceutical compositions of the present invention may be prepared by admixing the appropriate amount of glucosyl- β -cyclodextrin or maltosyl- β -cyclodextrin in water and adding thereto an antifungally effective amount of a compound of formulas I or II. Other excipients such as buffer or tonicity agents may be added and dissolved and additional water added to final volume. The resultant solution is sterile filtered and filled in to appropriate containers and sealed. Optionally, the water may be removed by well known methods, e.g. rotary evaporation or lyophilization. The dry powder may be reconstituted with water at a temperature of 15° to 35°C. The water is normally sterile water for injection and may contain pharmaceutically acceptable buffers, e.g., phosphate; citrate, as well as tonicity adjusting agents and preservatives.

Typically suitable tonicity adjusting agents include dextrose, mannitol, glycine and sodium chloride.

The desired pH is in the range of 3 to 8, especially 6-8.

The antifungally effective amount of a compound of formulas I or II is about 2mg/ml to 15 mg/ml and preferably is about 4 to about 12 mg/ml, more preferably about 10 mg/ml of solution.

The effective amount of glucosyl- β -cyclodextrin is about 50 to 250 mg/ml and preferably about 100 mg/ml to about 220 mg/ml, and more preferably about 200 mg/ml of water.

The effective amount of maltosyl- β -cyclodextrin is about 80 mg/ml to 400 mg/ml preferably about 100 mg/ml to 300 mg/ml and more preferably about 200 mg/ml.

Parenteral forms to be injected intravenously, intramuscularly, or subcutaneously are usually in the form of a sterile solution, and may contain salts or glucose to make the solution isotonic.

In general, the parenteral dosage for humans for antifungal use ranges from about 0.25 mg per kilogram of body weight per day to about 20 mg per kilogram of body weight per day, in single or divided doses, with about 0.5 to about 10 mg per kilogram of body weight per day being preferred.

The exact amount, frequency and period of administration of the compounds of the present invention for antifungal use will vary, of course, depending upon the sex, age and medical condition of the patient as well as the severity of the infection as determined by the attending clinician.

General Experimental

Example 1

Dissolve one g of 6-O-glucosyl- β -cyclodextrin (obtained from ENSUIKO Sugar Refining Co. Ltd., Yokohama 230 Japan) as mono-G1- β -CD) in 5 ml of distilled water to obtain a final concentration of 200 mg of 6-O-glucosyl- β -cyclodextrin per ml of water. Add and dissolve at room temperature 25 mg of the compound of formula II (which may be prepared in accordance with Example 30 of USP 5,661,151) in 2 ml of the above 6-O-glucosyl- β -cyclodextrin solution. Filter the resulting solution to obtain a clear solution containing 12.5 mg of compound of formula II per ml and 200 mg of 6-O-glucosyl- β -cyclodextrin per ml.

Examples 2-10

Table 1

Follow the procedure of Example 1 to determine the equilibrium solubility of the compound of formula II in solutions of various concentrates of 6-O-glucosyl- β -cyclodextrin at 5° and room temperature. The results are reported in Table 1.

TABLE 1

Equilibrium solubility of the compound of formula II in 6-O-glucosyl- β -cyclodextrin (G1- β -CD)

Conc. of G1 β -CD mg/mL	Solubility of the compound of Formula II (mg/mL)	
	@ Room Temperature	@ 5°C
30	0.5	0.5
40	1.1	0.9
50	1.0	1.2
100	3.8	4.8
200	12.5	11.9

Example 11

The stability of the compound of formula II in a solution containing about 2 mg of the compound of formula II per mL of a solution of 60 mg of 6-O-glucosyl- β -cyclodextrin per mL of distilled water for injection is at various pH was measured at 65°C. A phosphate buffer (20mM) was used to adjust the pH range from 6.0 to 7.4. The results are summarized in Table 2.

Table 2

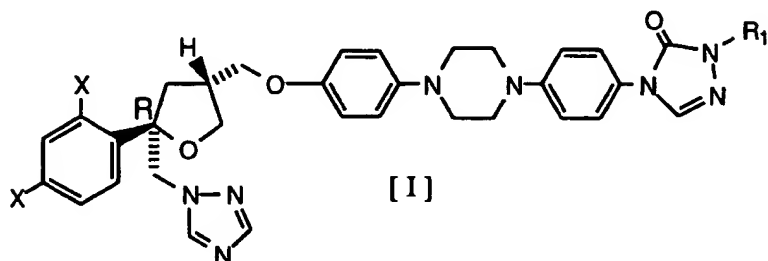
**STABILITY OF THE COMPOUND OF FORMULA II
IN AQUEOUS SOLUTION OF G1- β -CD AT 65° C**

Time, hrs	Conc. of the compound of formula II (mg/mL) in phosphate buffers (20mm)		
	pH = 6.0	pH = 6.5	pH = 7.4
Initial	1.7	1.9	1.6
15	1.7	1.8	1.5
39	1.6	1.9	1.5
109	1.7	1.8	1.5

Practically no increase in degradation products was observed with time.

What is claimed is

- (1) A pharmaceutical composition comprising
 (a) an antifungally effective amount of a compound represented by the formula I

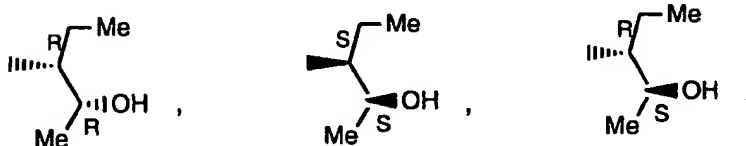


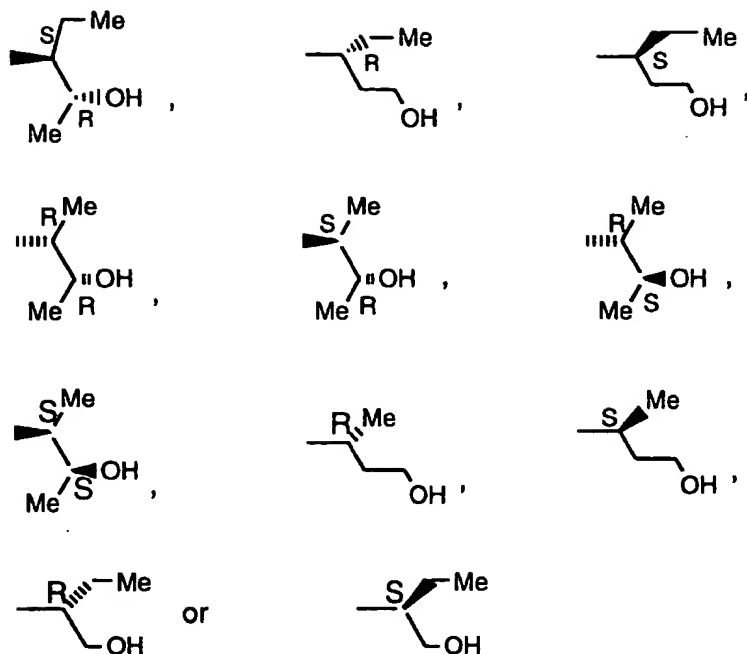
wherein X is independently both F or both Cl or one X is independently F and the other is independently Cl;

R₁ is a straight or branched chain (C₄- C₅) alkyl group substituted by a hydroxy moiety;

or a pharmaceutically acceptable salt thereof; and

- (b) an effective amount of one of maltosyl-β-cyclodextrin or glucosyl-β-cyclodextrin and
 (c) a pharmaceutically acceptable carrier
- (2) The pharmaceutical composition of claim 1 wherein R₁ is





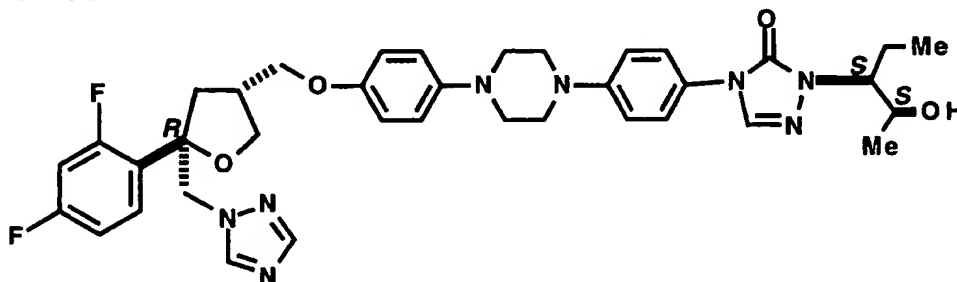
(3) The pharmaceutical composition of claim 1 wherein glucosyl- β -cyclodextrin is used.

(4) The pharmaceutical composition of claim 1 wherein maltosyl- β -cyclodextrin is used.

(5) The pharmaceutical composition of claim 1 wherein the pharmaceutically acceptable carrier is water.

(6) A pharmaceutical composition comprising

(a) an antifungally effective amount of the compounds represented by the formula II



or an ester of the OH group convertible in vivo into OH;
or a pharmaceutically acceptable salt thereof; and

(b) an effective amount of one of maltosyl- β -cyclodextrin or glucosyl- β -cyclodextrin and

(c) a pharmaceutically acceptable carrier.

(7) The pharmaceutical composition of claim 6 wherein the compound of formula II is used

(8) The pharmaceutical composition of claim 6 wherein maltosyl- β -cyclodextrin is used.

(9) The pharmaceutical composition of claim 6 wherein glucosyl- β -cyclodextrin is used.

(10) The pharmaceutical composition of claim 6 wherein the pharmaceutically acceptable carrier is water.

(11) The pharmaceutical composition of claim 6 which comprises 12.5 mg of compound of formula II per ml and 200 mg of 6-O-glucosyl- β -cyclodextrin per ml

(12) The pharmaceutical composition of claim 6 which adapted for parenteral administration.

(13) A method of treating a susceptible fungal infection in mammals which comprises administering to a mammal afflicted with such a fungal infection an antifungally effective amount of the pharmaceutical composition of claim 1.

(14) A method of treating a susceptible fungal infection in mammals which comprises administering to a mammal afflicted with such a fungal infection an antifungally effective amount of the pharmaceutical composition of claim 6.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/24938

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/495 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 661 151 A (SAKSENA ANIL K ET AL) 26 August 1997 cited in the application see column 58, line 19-24; claim 1 see abstract	1-14
Y	--- DUCHENE D ET AL: "PHYSICOCHEMICAL CHARACTERISTICS AND PHARMACEUTICAL USES OF CYCLODEXTRIN DERIVATIVES, PART II" PHARMACEUTICAL TECHNOLOGY, vol. 14, no. 8, August 1990, pages 22-22 - 26 - 28 - 30, XP002053301 see page 24, left-hand column, line 41 - page 24, right-hand column, line 3 -----	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

22 February 1999

Date of mailing of the international search report

16. 04. 99

Name and mailing address of the ISA

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Herrera, S

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/24938

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/24938

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5661151 A	26-08-1997	AU 681753 B	04-09-1997
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